IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of

Yuzo KAKIYA et al. Conf. No. 5540

Application No.: 10/565,105 Art Unit: 1624

Filed: January 19, 2006 Examiner: Noble E. Jarrell

For: PROCESS FOR PRODUCING IMIDE COMPOUND

DECLARATION

Honorable Commissioner for
Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Takashi BANDO, a citizen of Japan and residing at 1-12-24, Hinokuchi-cho, Nishinomiya-shi, Hyogo, Japan, declare and say that:

1. I have majored in Chemistry and received the degree of Master from Depatment of Engineering, Kyoto University in Japan in 1988.

I am a synthetic chemist and since 1988 up till the present, I have been an employee of Dainippon Sumitomo Pharma Co. Ltd. (former Sumitomo Pharmaceutical Company Limited) and has been engaged in research and development of medicaments in said company.

I have received the degree of Doctor of Philosophy from Department of Engineering, Nagasaki University in 1994.

2. I have read the description and claims of the instant U.S. Patent Application No. 10/565,105 and am familiar with the subject matter

thereof, and also have read an outstanding Office Action on the merit dated January 30, 2008 and further the cited Saji et al., US 5,532,372 and am familiar with the subject matter thereof.

3. Under my direction, the following experiments have been done for the purpose of studying the quality and yield of the desired imide compound hydrochloride prepared by the method disclosed in Example 1-(d) of Saji et al. reference as well as those of the desired imide compound hydrochloride prepared by the method of the present invention, and comparing the quality and yield of the compounds prepared by both methods, and further for studying the effects of variety of the concentration of the aqueous hydrochloric acid solution to be used in the procedure of producing the desired imide compound hydrochloride on the quality and yield of the product.

(1) Experiment 1

I. Preparation of (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benz-isothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo-[2.2.1]heptanedicarboxyimide hydrochloride:

A) Method of Saji et al., US 5,532,372

According to the method of Example 1-(d) of Saji et al. reference, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl-methyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide hydrochloride was prepared as follows.

To a solution of (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benz-

isothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo-[2.2.1]heptanedicarboxyimide (10.7 g) in acetone (54 ml, 42.7 g) was added 13.7% 2-propanol solution of hydrogen chloride (6.38 g), and the mixture was stirred at 20°C to 30°C for two hours. Precipitated crystals were collected by filtration and dried under reduced pressure to give crystalline (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzisothiazol-3yl)-1-piperazinyl-methyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide hydrochloride in the yield as shown in Table 1.

B) Method of the present invention

According to the method of Example 10 of the present Application No. 10/565,105, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptane-dicarboxyimide hydrochloride was prepared as follows.

(1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinylethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxy-imide (8.25 g) was dissolved in acetone (102 g) with heating under reflux to give an acetone solution thereof. To this acetone solution was added dropwise a 5.0 % aqueous hydrochloric acid solution (1.1 equivalent) at about 55°C over a period of one hour. Then, the mixture was stirred at about 60°C for one hour. The reaction mixture was cooled to 0°C, and stirred at the same temperature for one hour. The mixture was filtered, and the resulting solid was dried at room temperature under reduced pressure to give crystalline (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benziso-thiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]-

heptanedicarboxyimide hydrochloride in the yield as shown in Table 1.

II. Analysis of the impurities of the crystalline product:

The impurities of the products obtained in the above Experiment 1-I-A) and 1-I-B) were measured by liquid chromatography (HPLC) under the following conditions:

Column: YMC Pack Pro C18 (5 μm, 6 mmø x 15 cm) (YMC Co., Ltd.)

Mobil phase: A: A mixture of 5 mmol/L phosphate buffer (pH 7.0) and acetonitrile (4 : 1)

B: Acetonitrile

Gradient time program condition

Wavelength: 230 nm

III. Analysis of acetone of the crystalline product:

The acetone content of the product obtained in the above Experiment 1-I-A) and 1-I-B) was measured by gas chromatography under the following conditions:

Detector: A hydrogen flame ionization detector

Column: OVI-G-43 (0.53 mmø x 30 m, 3 μm film thickness) (SUPELCO)

Column Temperature: Time program condition of raising temperature

Carrier gas: Helium

Detector temperature: about 200°C

With respect to the product in the above Experiment 1-I-A), the content of 2-propanol was also analyzed likewise.

III. Results

The above results are shown in the following Table 1.

	Experiment 1-I-A)	Experiment 1-I-B)
Method for production	Ex. 1-d) of Saji et al.	Ex. 10 of this invention
Starting material	10.7 g	8.25 g
Aqueous HCl solution	13.7%HCl/2-propanol(6.38g)	5.0% HCl solution (13.3g)
Amount of acetone	54 ml (42.7 g)	102 g
Drying	under reduced pressure	under reduced pressure
Yield (% by weight)	11.47 g (99 %)	7.97 g (90 %)
Amount of impurities (% by weight)	0.22 %	0.04 %
amount of Acetone (% by weight)	1.73 %	0.04 %
Amount of 2-propanol	N.D. (detection limit: 0.05%)	-

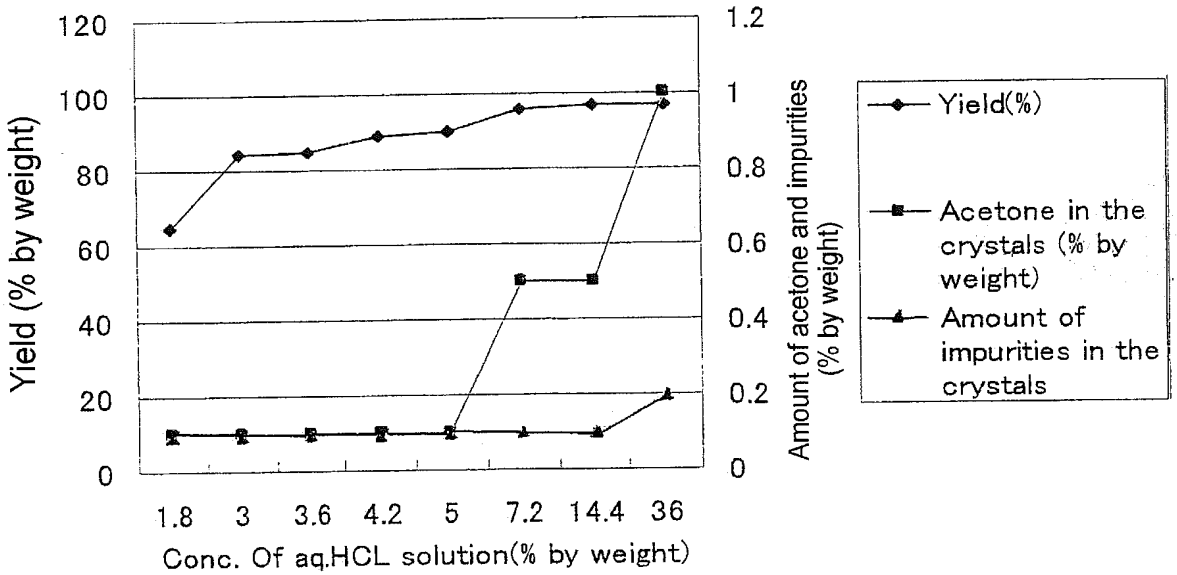
As is clear from the above results, according to the method of the cited Saji et al. reference, the obtained imide compound hydrochloride has much impurities like 0.22 % by weight and also a high amount (1.73 % by weight) of acetone while the 2-propanol could be removed to less than the detection limit. On the other hand, according to the method of the present U.S. Patent Application No. 10/565,105, the desired imide compound hydrochloride could be obtained in high purity, that is, having much less impurities content of such remarkably smaller as 0.04 % by weight and also much less residual acetone (0.04 % by weight) in comparison with the product prepared by the method of Saji et al.

(2) Experiment 2

The desired (1R,2S,3R,4S)-N[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptane-dicarboxyimide hydrochloride was prepared in the same manner as in Experiment 1-I-B) excepting using various concentrations of the aqueous

hydrochloric acid solution in the ranges of 1.8 to 36 % by weight (i.e. 1.8, 3.0, 3.6, 4.2, 5.0, 7.2, 14.4 and 36.0 % by weight), and thereby effects of concentration of the aqueous hydrochloric acid solution on the quality and yield of the product were studied.

The results are shown in the following Figure 1.



As is clear from the above results, when the aqueous hydrochloric acid solution in the range of 1.8 to 5.0 % by weight was used, the product had very low impurities, but with increase of the concentration of hydrochloric acid, the product had increased amount of impurities. Furthermore, when the aqueous hydrochloric acid solution in the range of 1.8 to 5.0 % by weight was used, the product had very low acetone content (low residual solvent), and with increase of the concentration of hydrochloric acid, the product had increased amount of acetone, too, while the yield of the product did not so significantly vary even by varying the concentration of hydrochloric acid solution.

4. It is my opinion based on my knowledge and experience in this field that the desired imide compound hydrochloride, (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]2,3-bicyclo[2.2.1]heptanedicarboxyimide hydrochloride is useful as a psychotropic medicament, that is, as a drug for the treatment of schizophrenia, and that in order to use a compound as a drug, it is required to have an extremely high purity in view of safety and hence if the product contains impurities or remaining solvents which are used in the preparation procedure, it shall be removed by purification,

and that according to the process as disclosed in the cited Saji et al., US 5,532,372, the product has remaining solvents, impurities, etc. and hence is not suitable for use as a drug and further, since the imide compound hydrochloride is hardly soluble in a solvent and is very difficult to purify by the conventional purification methods such as recrystallization, column chromatography, etc., it is very important to produce a highly pure product without necessity of any specific purification method,

that on the contrary to the method of Saji et al. reference, the method of the present invention is very useful as a method for industrial production of the imide compound hydrochloride since it can give the desired imide compound hydrochloride having high purity with high yield without necessity of any specific purification method, that is, the method of the present invention can give the desired imide compound hydrochloride having much less impurities and much less content of the residual solvent in

comparison with a known method as disclosed in the cited Saji et al.,

and further that it is very important to control the conditions of aqueous hydrochloric acid solution to be used in the procedure for preparing the hydrochoride salt from the free imide compound to the specific range of 1.8 to 5.0 % by weight as defined in claim 1 of the instant U.S. Patent Application No. 10/565,105 for the purpose of producing the desired imide compound hydrochloride having high purities, less residual solvent with keeping a high yield, which characteristic feature is not taught or even suggested by Saji et al. reference.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This day of April, 2008

Takashi Bando